REMARKS/ARGUMENTS

By this Amendment, claims 1 and 88 are amended. Claims 5, 6, 15, 17-25, 35-40, 46, 47, 53, 57-68, 74 and 87 have been withdrawn from consideration pursuant to a restriction requirement by the Examiner. Claim 84 is "constructively" canceled since it was inadvertently omitted from the original claim listing and never presented. Claims 1, 3-4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82-83, 85-86, and 88 are pending.

The Examiner's courtesy in granting an interview to the inventors Drs. Wickstrom and Thakur and their representative Marina Volin on February 21st, 2007 is gratefully acknowledged. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

Support for amending claims 1 and 88 can be found in the original disclosure, e.g., on page 12, lines 1-6 and page 18, lines 3-10.

Entry of this Amendment is proper under 37 C.F.R. §1.116 because the Amendment: (a) places the application into condition for allowance (for reasons discussed herein), (b) does not raise any new issues requiring further search and/or consideration (because the Amendment is directed to subject matter previously considered during prosecution), (c) does not present any additional claims without canceling a corresponding number of finally rejected claims, and (d) places the application into better form for appeal, should an appeal be necessary. The Amendment was not previously made because the form of the Amendment was not determined until the telephonic interview. Applicants respectfully request entry of the Amendment.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claim Objections

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82, 83, 85, 86, and 88 are objected to because the instant claims recite a targeting moiety capable of binding a cell surface molecule and the redundant recitation of the targeting moiety being bound by a cell surface molecule (see section 10 of the Office Action).

Base claims 1 and 88 are amended to remove the phrase "being bound by a cell surface molecule" to speed up the resolution of this matter.

Claim Rejections: 35 USC § 103

103(a) rejection over Tomalia et al. (U. S. Patent No. 5,714,166) in view of Meade et al. (US Patent No. 6,713,046)

Claims 1, 4, 7-14, 16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 remain and the new claim 88 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., as applied to claims 1, 2, 4, 7-10, 12-14, 16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 above, in view of Meade et al. (US Patent No. 6,713,046) (see section 9 of the Office Action).

This rejection is respectfully traversed. Base claims 1 and 88 as amended obviate the rejection under 35 U.S.C. 103(a).

Covalent bonding

Base claims 1 and 88 are amended to specify that the term "conjugating" means "covalently conjugated".

No Covalent Association between a Genetic Material and a Dendrimer

Tomalia et al. does not teach covalent association between a genetic material and a dendrimer. In column 17, lines 41-67, a generic definition is given to the term "associated with"

as follows:

> As used herein, "associated with" means that the carried material(s) can be physically encapsulated or entrapped within the core of the dendrimer, dispersed partially or fully throughout the dendrimer, or attached or linked to the dendrimer or any combination thereof, whereby the attachment or linkage is by means of covalent bonding, hydrogen bonding, adsorption, absorption, metallic bonding, van der Waals forces or ionic bonding, or any combination thereof.

This is a general statement listing all envisioned kinds of bonding. However, further in the specification, Tomalia et al. restricted the types of association between dendrimer and "genetic materials" (which include PNA) to exclude covalent bonding (see column 47, lines 55-62):

> The conjugates of genetic material and dendrimer are referred to as complexes. A "complex" as that term is used herein refers to a type of conjugate of dendrimer and carried material in which association between the carried material and the dendrimer is effected through ionic bonding, van der Waals forces, hydrogen bonding, metallic bonding, or any combination thereof. In a complex, the carried material is not associated with dendrimer through covalent bonding (emphasis added).

The other recitations of the (T)e*(P)x*(M)y structure (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in claims, not in background, not in examples.

It would be unobvious to use covalent bonding between dendrimer and genetic material because Tomalia et al. teach away from covalent association in complexes when genetic material is concerned and consequently, a person skilled in the art would not be motivated to utilize covalent bonding between dendrimer and genetic material, such as, PNA.

Arrangement of Components

On page 5, the Examiner stated that "Tomalia et al. teach a compound with the formula T-L1-P-L2-M, wherein M represents a PNA, T represents a targeting moiety that can bind a cell-surface molecule, P represents a dendrimer, and wherein M and T are associated with P via identical or different linkers, LI and L2 (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60)."

Tomalia et al. do not teach linkers LI and L2 and teach a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52), (column 18, lines 23-67), (column 19, lines 1-67), (column 20, lines 1-29), (column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds.

Applicants teach a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as, for example, a radionuclide chelated to a dendrimer, P represents a PNA that can bind a nucleic acid, and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule, and wherein X, P and T are associated with identical or different spacers L1 and L2 to prevent steric hindrance (see page 18, lines 3-10 of the specification). Having the spacers between the components is a non-obvious solution to the problem of steric hindrance between the three functional units of the compound which is neither recognized nor taught by Tomalia et al.

On page 6, the Examiner stated that "Tomalia et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, as stated above, Tomalia et al. teach all components necessary for this arrangement."

However, it is not enough to have a disclosure of components. The order of functional

units in the compound X-L1-P-L2-T is vital to the purpose of entering a cell, then binding to a nucleic acid target. As stated on page 5 of the specification

> It has now been discovered that a compound comprising a diagnostic or therapeutic moiety can be retained inside a cell by conjugating the moiety to at least one PNA that is targeted to the transcripts from one or more genes of interest. The diagnostic or therapeutic moiety is also conjugated to at least one targeting moiety specific for an extracellular receptor or other cell surface molecule. The targeting moiety binds to the surface of a cell, and the entire compound is then internalized. Once inside the cell, the PNA portion of the diagnostic or therapeutic compound binds to RNA transcripts in a sequence specific manner. Binding of the PNA to its target RNA transcript retains the compound within the cell. The PNA can be designed to bind to a predetermined nucleic acid sequence from an RNA transcript, for example a mutated or overexpressed sequence that is characteristic of a pathological state.

The compound $(T)_e*(P)_x*(M)_y$ taught by Tomalia et al. permits compound binding to multiple neighboring cells via multiple T2 interactions on the surface of the dendrimer P, preventing internalization of the compound into a single targeted cell, which in turn will prevent T1 binding to the targeted nucleic acid inside the cell.

Further, following this reference, one of ordinary skill in the art would have lacked motivation to use its teachings alone or in combination with the teachings of the secondary reference to make the compound of the present invention with a reasonable expectation of success. Absent such reasonable motivation, there can be no prima facie case of obviousness. See, e.g., MPEP §2143. There is no motivation in Tomalia et al alone or in combination with Meade et al. to change the order of components to yield the compound of the invention because neither reference recognized the need to covalently connect a dendrimer with the PNA portion and then with the cell surface targeting moiety to retain the compound within the cell (for detection or therapeutic purposes). The secondary reference Meade et al. does not remedy the

aforementioned deficiency of the primary reference, the Tomalia et al. reference, to teach or suggest all the limitations of the base claims 1 and 88 because Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Moreover, it would not be obvious to a person skilled in the art to substitute DNA with PNA and have a reasonable expectation of success because PNA is insoluble in water and aggregates easily.

The proposed combination of Tomalia et al. and Meade et al. fails to render base claims 1 and 88 obvious. Thus, it would not be obvious to the ordinary skilled artisan to vary the arrangement. Without such motivation, there is no *prima facie* case of obviousness.

Claims 4, 7-16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 depend from base claim 1 and are unobvious over the Tomalia et al. reference in combination with the Meade et al. reference for at least the same reasons base claim 1 is unobvious.

Accordingly, reconsideration and withdrawal of the Section 103 (a) rejection of claims 1, 4, 7-16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, 86 and 88 are respectfully requested.

103 (a) rejection over Lewis et al., in view of Liang et al. and Basu et al.

Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (2002, cited on form PTO-892 on 05/16/2006), in view of Liang et al. (Molecular Therapy, 2000, 3:236-243), as evidenced by Basu et al. (1997, cited on form PTO-892 on 05/1 6/2006) (see section 12 of the Office Action).

This rejection is respectfully traversed.

The Examiner acknowledged that Lewis et al. "do not teach a targeting moiety capable of binding to a cell surface molecule (claim 1)" (see pages 7 and 8 of the Office Action).

The Liang et al. reference is relied upon to remedy the deficiency of Lewis et al. to yield the invention. Liang et al. teach construction of a transferrin-PNA conjugate associated with a plasmid DNA vector for the purpose of plasmid DNA vector delivery into cells to effect gene therapy. Liang et al. reported no cellular uptake of the transferrin-PNA:DNA. Therefore Liang et al. provide no motivation toward the design of the present diagnostic compound. Liang et al. did observe that the cationic polymer polyethyleneimine, associated with a plasmid DNA vector, enabled cellular uptake. Liang et al. further reported enhanced vector-encoded enzymatic activity in transfected cells if transferrin-PNA was associated with the plasmid DNA vector:polyethyleneimine complex, but reported no control with a comparable protein-PNA conjugate. The toxicity of polyethyleneimine, however, teaches away from utilizing their construct in a human. Finally, transferrin is so large, its binding to its receptor is so strong, and the transferrin receptor is so ubiquitous, that all cells would take up transferrin and any other moiety conjugated to it, regardless of the presence or absence of the target nucleic acid in a cell. Thus, in the absence of motivation, the teaching of Lewis et al. cannot be modified to yield the present invention. If both references are combined as suggested by the Examiner, they still would not yield the invention. Therefore, base claim 1 and 88 are unobvious in light of a combination of all named references.

Claims 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 depend from base claim 1 and are unobvious over the Lewis et al. reference in combination with the Liang et al. reference for at least the same reasons base claim 1 is unobvious.

Accordingly, reconsideration and withdrawal of the Section 103 (a) rejection of claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 and 88 are respectfully requested.

103(a) rejection over Lewis et al. taken with Liang et al. and Basu et al., in further view of

Nakano et al. (2001, cited on form PTO-892 on 05/16/2006)

Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 80, 82, 83, 85, and 86 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., as applied to claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 above, in further view of Nakano et al. (2001, cited on form PTO-892 on 05/16/2006) (see section 14 of the Office Action).

Lewis et al. and Liang et al. are discussed above. Nakano does not cure the deficiency of the combined references to teach or suggest all the limitations of the base claim 1 because Nakano, et al. teach multiple intratumoral injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice. Further, Nakano, et al. do not teach probe (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular cytoplasm, or probe binding to mRNA in cellular cytoplasm.

Therefore, base claim 1 is unobvious in light of a combination of all named references. Claims depended from claim 1 are therefore unobvious.

103(a) rejection over Lewis et al. taken with Liang et al. and Basu et al., in further view of Tomalia et al

Claims 1, 3, 4, 28-32, 34, 41-45, 48-52, 69, 71-73, 80, 83, 85, and 86 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., as applied to claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 above, in further view of Tomalia et al. (see section 15 of the Office Action).

As the Examiner stated on page 10, "Lewis et al. taken with Liang et al. and Basu

et al. do not teach a dendrimer (claim 43) or a plurality of chelants optionally complexed to one or more diagnostic metal ions (claims 44 and 45)." Tomalia et al. teach that PNA can be conjugated to dendrimers or a plurality of dendrimers, i.e., a plurality of chelants (column 3, lines 22-40, column 13, lines 5-11, column 41, lines 28-34, column 45, lines 1-9, column 47, lines 1-10) for delivery of diagnostic compounds, such as Gd(III) into cells.

However, as discussed above, Tomalia et al. does not teach covalent association between a genetic material and a dendrimer. Further, Tomalia et al. does not teach specific arrangement of components as in the compound of the invention, i.e., X-L1-P-L2-T. The motivation to modify the references to make this arrangement cannot be found in either of the references cited and cannot come from the invention. Thus, even if combined, the references fail to teach or suggest all the claim limitations of base claims 1 and 88.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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